

**REMARKS**

Applicants request entry of this Amendment and Response. Applicants request reconsideration of the rejection of the claims. Claims 1-3, 5-14, and 19-22 are pending in the application.

Claim 1 has been amended to incorporate the limitations of claim 19. Claim 20 has been amended to clarify the subject matter of the claim. No new matter is added by the amendments.

Claim 19 has been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of this claim in a continuation application.

**35 U.S.C. § 101**

Claims 1-3 and 5-14 stand rejected under 35 U.S.C. § 101 for alleged lack of utility. Applicants respectfully traverse this rejection.

In order to reject claims under 35 U.S.C. 101, the Examiner must (A) make a *prima facie* showing that the claimed invention lacks utility, and (B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing (MPEP 2107.02 IV., citing *In re Gaubert*, 524 F.2d 1222, 1224 (CCPA 1975). An Applicant's assertion of utility normally creates a presumption of utility, and to overcome this presumption, the Examiner bears the burden of establishing that it is more likely than not that one of ordinary skill in the art would doubt the truth of the asserted utility. MPEP 2107.02 III. A. The Examiner is reminded that the courts "have consistently reversed rejections by the Office asserting a lack of utility for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence that reasonably supports such a utility. In view of this, Office personnel should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility." MPEP 2107.03.

Applicants' claims are directed to an isolated library of structurally constrained peptides, wherein each cyclic peptide comprises an amino acid sequence C1-A1-A2-(A3)<sub>n</sub>-A4-A5-C2 (SEQ ID NO: 1). The peptide library can be screened against biological molecules to identify members of the library that bind to a particular biological molecule. A subset of residues within a peptide member of the library is varied to mimic various bioactive peptides having an

identified secondary structure, such as a  $\beta$ -turn, which has proven significant in many biological processes. As such, the peptide library of the invention can be used to screen a wide variety of biological molecules to identify peptides that may bind and effect the function of the biological molecules. The peptide library can also be used inter alia, to screen for biologically active molecules including agonists and antagonists.

At page 23, lines 12-14, Applicants assert that the peptides generated according to the methods of the invention can be candidates for therapeutic agents including enzyme inhibitors, ligand antagonists, ligand agonists, toxins and immunogens. Thus, Applicants have asserted a specific utility resulting in a presumption of utility under 35 U.S.C. 101, at least for this reason. Applicants respectfully submit that the Examiner has not met his burden of overcoming this presumption of utility. In the previous response filed December 26, 2002 (hereby incorporated by reference), Applicants provided specific examples from the specification in support of the utility of the claimed libraries.

The Examiner is now understood to argue that while the compounds of the library of constrained peptides possess utility, the claimed library itself does not possess utility. Applicants respectfully disagree. Applicants submit that libraries of such peptides have a well-established utility.

The existence of commercial available peptide libraries belies the Examiner's assertion that such libraries lack utility and shows that such libraries have a well-established utility. Morphosys, Inc., for example, provides Human Combinatorial Antibody Libraries (HuCAL) for the in vitro generation of highly specific and fully human antibodies. Multiple pharmaceutical and biotechnology research companies have incorporated Morphosys' libraries into their R&D processes, including Bayer, Biogen, Bristol-Myers Squibb, Centocor/Johnson&Johnson, Immunogen, Oridis, Roche, Schering, and Xoma. Thus, libraries of peptides are clearly capable of having significant utility in the area of biotechnology and pharmaceutical research as a result of the utilities of the individual members of the libraries.

Furthermore, the U.S. Patent & Trademark Office has routinely granted patents to libraries of compounds. *See, e.g.*, U.S. Pat. No. 6,482,591 (claims to synthetic conformationally-restricted probe libraries), and U.S. Pat. No. 6,475,806 (claims to libraries of fusion proteins). Further, Applicants submit that it is routine for the USPTO to find sufficient utility for, and grant

patents on, claims to libraries of compounds wherein the utility lies in the ability to screen the library for compounds that can bind to specific target molecules.

In addition, as argued previously, the library is useful to identify peptides that can bind to a variety of target molecules such as HIV gp120, human IgE Fc receptor, and EPO agonists EMP1. Applicants have also identified 12 clones that bind to Fc IgE receptor 1. Thus, Applicants have demonstrated that the library is useful to identify one or more peptides that bind to a target antigen. Such peptides can be useful as agonists or antagonists of the target molecules.

In light of the foregoing arguments, Applicants submit that the claimed libraries possess utility satisfying the requirements of 35 U.S.C. 101. Applicants have asserted a specific utility for members of the library as discussed above, thus creating a presumption of sufficient utility for the claimed libraries. In addition, Applicants submit that libraries of peptides have a well-established utility. Therefore, Applicants respectfully request withdrawal of this 35 U.S. C. 101 rejection.

**35 U.S.C. §112, first paragraph**

**Written Description**

Claims 1-3, 5-14, and 19-22 stand rejected as containing subject matter not described in the specification. Applicants respectfully traverse this rejection.

As discussed in MPEP 2163.02, the standard for determining whether an application complies with the written description requirements of § 112, first paragraph, is whether the description clearly allows persons of ordinary skill in the art to recognize that the inventor was in possession of the claimed subject matter as of the filing date. Further, "a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption." MPEP 2163.04. A number of factors can be utilized to establish written description including:

- a) full or partial structure;
- b) physical and/or chemical properties;
- c) functional characteristics;
- d) known or disclosed correlation between structure and function;

- e) methods of making; and
- f) combinations of A-E.

As stated in Applicants' previous response, the specification clearly provides an adequate written description for the claimed library under these factors. Applicants have described the structure of their library of peptides, including their physical and/or chemical properties, and provided several examples of the peptides in the library. See, e.g., Example 1, where Applicants describe synthesizing a peptide and analyzing its properties via NMR spectroscopy. Applicants have further described the functional characteristics of members of the library, and disclose correlations between their structure and their function. In Examples 1-2, for instance, Applicants demonstrate that peptides of the library function as scaffolds that successfully stabilize secondary structures of native bioactive proteins. Examples 3-4 detail correlations between the selection of specific amino acid residues at specific locations, and the resulting ability of the peptide to stabilize hairpin turns. Finally, Applicants provide extensive information on methods of generating the peptide libraries of the invention (Part IV, pages 15-23).

Moreover, Applicants have in fact described how the library of peptides are used. The Examiner is directed to the arguments made above with respect to the utility rejection. Applicants have disclosed that the peptide library is useful for designing ligands that mimic native bioactive proteins in binding to specific targets, and have provided working examples in support of this disclosure. Applicants have also shown that members of the peptide library closely mimic native proteins of known activity, including agonist activity. Applicants also submit that libraries of peptides have well-established utilities in the art.

For the foregoing reasons, Applicants submit that the specification provides an adequate written description for the claimed library. Accordingly, withdrawal of this rejection is requested.

The Examiner also maintains that there is no support for an "isolated" library in claim 1 nor "isolated plurality" in claim 20. Applicants respectfully disagree. Under 35 U.S.C. 112, the specification of a patent must contain a written description of the invention that conveys to one of ordinary skill in the art that the Applicant was in possession of the claimed invention. The disclosure does not have to describe exactly, in *ipsis verbis*, the subject matter claimed. *In re*

*Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). Rather, the rule is that one of ordinary skill in the art must be able to recognize that the Applicant invented that which was claimed. *Id.*

Claim 1 recites an isolated library of structurally-constrained cyclic peptides, wherein each cyclic peptide comprises an amino acid sequence C1-A1-A2-(A3)<sub>n</sub>-A4-A5-C2. Claim 20 recites an isolated plurality of cyclic peptides having a reverse turn secondary structure, wherein each cyclic peptide comprises the amino acid sequence C1-A1-A2-(A3)<sub>n</sub>-A4-A5-C2. Applicants submit that one of ordinary skill in the art would readily recognize from the specification that Applicants were in possession of this isolated library.

The specification discloses that the peptide libraries of the invention are isolated. In Example 5, for instance, Applicants disclose the construction of phage-displayed libraries based on a trp peptide scaffold. In Example 6, the phage libraries are used to select for peptides that bind to a target receptor. The assay comprised screening for binding to the receptor by incubating phage supernatant containing the peptides with plates coated with the receptor. Applicants submit that a supernatant, by definition, comprises a component that has been separated from, and hence isolated from, another component. Applicants submit that phage supernatant comprises a library of peptides that has been separated, and, therefore, isolated from a more heterogeneous mixture from which the supernatant was generated. Since no *ipsis verbis* description of "isolated" is required in the specification to support this language in the claims, Applicants submit that there is ample support for the "isolated" language of claims 1 and 20.

The Examiner states that "synthetic" amino acids as recited in claim 20 is not supported by the specification. Amended claim 20 does not recite "synthetic" amino acids.

The Examiner asserts that "inclusive" as recited in claim 20 is not supported. Applicants respectfully disagree. As stated above, the specification need not literally describe in *ipsis verbis* the language recited in the claims. Rather, one of skill in the art must be able to recognize from the specification that Applicants were in possession of the claimed invention. Claim 20 recites that "(A3)<sub>n</sub> is a library of natural amino acids where n is 3 to 12, inclusive." Support for this language is found at page 10, lines 2-3 of the specification, which states that "A3 is any naturally occurring L-amino acid and n is an integer that is selected from the group consisting of 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12." Applicants submit that the specification, therefore, clearly indicates that the integer n can be any number from 3-12, including 3 or 12, i.e., 3-12 inclusive. One of skill in

the art would readily recognize, therefore, that Applicants were in possession of an isolated plurality of cyclic peptides wherein n is 3-12 inclusive.

Based on the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph rejections of claims 1-3, 5-14, and 19-22.

**35 U.S.C. § 112, Second Paragraph**

Claims 1-3 and 5-14 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner maintains that in claim 19, the phrase "the amino terminus of C1 is optionally protected" broadens the base claim 1. Although Applicants do not agree with the propriety of this rejection, claim 1 has been amended to accommodate the Examiner's suggestion to incorporate the limitation of claim 19. Accordingly, claim 19 has been cancelled.

The Examiner maintains it is not clear as to the library that is screened to isolate the claimed library. Applicants submit that the present invention does not comprise screening a library in order to isolate the claimed library, and that neither the claims nor the specification recite any such requirement.

The Examiner maintains that claim 20 is duplicative of claim 1. Applicants respectfully disagree. Claim 1 recites that A2 and A4 are independently amino acids W, Y, F, H, I, V, or T. Claim 20, however, recites that A2 and A4 are independently amino acids W or L. Therefore, Applicants submit that claims 1 and 20 are not duplicative.

Based on the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph rejections of claims 1-3 and 5-14.

**35 U.S.C. § 102**

Claims 1-2, 4, 5, 8, and 9 stand rejected under 35 U.S.C. § 102(e) as anticipated by Wrighton et al. The Examiner asserts that the subgeneric formulas disclosed in Wrighton with A1 defined as W, H, and L together with the species included in the subgenus fully meets the claimed invention.

As Applicants stated in the previous response, Wrighton et al. do not disclose at least the element that each cyclized peptide in the library comprises a sequence C1-A1-A2-(A3)<sub>n</sub>-A4-A5-C2. Applicants' claims are directed to a library in which each of the peptides comprise a specific set of amino acids where A1 and A5 are W, Y, F, H, I, V, or T and A2 and A4 are W, Y, F, L, M, I, or V. The libraries of Wrighton I and II contains peptides outside of this requirement and, therefore, do not teach this element of the claimed invention. For example in Wrighton I, in the positions analogous to A1 and A5 in the Wrighton I library, A1 must be R, H, L, or W, and A5 must be D, E, I, L or V. *See* Wrighton I, col. 169, lines 1-12 and Fig. 2-1 and 2-2.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See* MPEP 2131.01, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in the same complete detail as is recited by the claims. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Since Wrighton et al. do not disclose a library having each and every limitation of Applicants' claimed libraries, Wrighton et al. cannot anticipate the claims. Applicants submit that the claims are patentable over Wrighton et al. under 35 U.S.C. 102 at least for this reason.

The Examiner now cites to *In re Petering*, 133 USPQ 275 (CCPA 1962), for the proposition that if one of skill in the art is able to at once envisage the specific compound within a generic chemical formula, the compound is anticipated. However, Applicants submit that one of skill could not at once envisage the claimed compounds from the chemical formula disclosed in Wrighton et al.

In *In re Petering*, the appellants claimed a genus of isoalloxazine structures. The prior art disclosed a genus of isoalloxazine structures encompassing the compounds falling within the scope of appellants' claims. The court did not find, however, that the prior art genus anticipated appellants' claims on this basis alone. Indeed, the court explicitly stated that the prior art "encompasses a vast number and perhaps even an infinite number of compounds . . . Even though appellants' claimed compounds are encompassed by this broad generic disclosure, we do not think this disclosure by itself *describes* appellants' invention, as defined by them in any of the appealed claims, within the meaning of 35 U.S.C. 102(b)." *Id.* at 279.

The *In re Petering* court found that the prior art anticipated the claims only because within this broad disclosure of generic isoalloxazines, the reference additionally disclosed specific preferences for five different substituent groups, through a listing of preferred R groups and eight specific isoalloxazines. *Id.* The court found that this disclosed subgenus of specific preferences contained only 20 compounds, and that one of skill in the art reading the reference, including the disclosed subgenus, would have at once envisaged the claimed compounds. *Id.* at 280. Applicants submit that from the description of Wrighton et al, one of skill in the art would not envisage a library wherein each cyclized peptide comprise specific amino acids where A1 and A5 are W, Y, F, H, I, V or T and A2 and A4 are W, Y, F, L, M, I, or V.

The mere disclosure in the prior art of a genus does not by itself anticipate a claim to a subgenus falling within that genus. In *Ultradent Products Inc., v. Life-Like Cosmetics Inc.*, 44 USPQ2d 1336 (Fed. Cir. 1997), for example, the court found that wherein the claims recited a composition containing 3% or 5% carboxypolymethylene, the claims were not anticipated by prior art disclosing a range of 0.05% to 5% carboxypolymethylene. The court stated that there are many possible compositions within the range disclosed in the prior art, and that for anticipation to occur, the prior art must describe to one of skill in the art "combinations meeting the limitations of the claims, from among the many possible candidates." *Id.* at 1342.

The peptide formulas disclosed in Wrighton et al., and that the Examiner asserts anticipate Applicants' claims, comprise a very large number of possible peptides. Therefore, one of ordinary skill in the art would not find any direction in Wrighton et al. to develop the library of disclosed peptides where each member of the library has a sequence as required by Applicants' claims. Claims 1-2, 4, 5, 8, and 9, therefore, are patentable over Wrighton et al. under 35 U.S.C. 102 for this additional reason.

In light of the foregoing arguments, Applicants respectfully submit that the claims are clearly patentable over Wrighton et al. under 35 U.S.C. 102. Withdrawal of the rejection is requested.



**35 U.S.C. § 103(a)**

The Examiner rejected claims 1, 2, 4, 5, 8, and 9 under 35 U.S.C. § 103(a) as being obvious over Wrighton et al or Wrighton et al. The Examiner asserts that the libraries disclosed in either Wrighton et al. render the claimed library *prima facie* obvious. Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, the Examiner must show a) that the references disclose all of the elements of the invention, b) that there would be motivation to combine the references to modify the teaching of the reference to obtain Applicants' claimed invention, and c) a reasonable expectation of success. Applicants submit that the Examiner has not established a *prima facie* case of obviousness at least because the references do not disclose all of the elements of the claimed invention, and there is no motivation provided in the references to modify the teachings of the cited references to obtain Applicants' claimed invention.

As discussed previously, Wrighton et al. do not disclose at least the element that each cyclized peptide in the library comprises a sequence C1-A1-A2-(A3)<sub>n</sub>-A4-A5-C2 having the amino acids recited in the present claims. Applicants' claims require all cyclized peptides in the library to comprise a specific set of amino acids where A1 and A5 must be W, Y, F, H, I, V, or T and A2 and A4 must be W, Y, F, L, M, I, or V. The libraries of Wrighton I and II contains peptides outside of this requirement. For example in Wrighton I, in the positions analogous to A1 and A5 in the Wrighton I library, A1 must be R, H, L, or W, and A5 must be D, E, I, L or V. See Wrighton I, col. 169, lines 1-12 and Fig. 2-1 and 2-2. In Applicants' claimed library A1 cannot be R or L and A5 can never be D or E.

As stated previously with respect to the argument against the 35 U.S.C. 102 rejection, Applicants' claims are directed to libraries of peptides comprising amino acid sequences designed to stabilize secondary structures. Wrighton et al. nowhere teach or suggest the significance of selecting amino acid sequences to stabilize and present a wide variety of secondary structures. Therefore, Wrighton et al. provide no teaching or suggestion to modify the peptide formulas disclosed in that reference so that each cyclized peptide has the amino acid sequence recited in Applicants' claims. Wrighton et al. provide no teaching that, out of the very large number of disclosed peptides therein, any of the peptides should be modified to produce the particular genus of peptides disclosed in the present claims. One of ordinary skill in the art,

reading Wrighton et al., would not be motivated to modify the disclosed peptides to produce the peptides of the libraries recited in the present claims. Nor has the Examiner provided any such motivation. Thus, Applicants submit that the Examiner has not established a *prima facie* case of obviousness.

Accordingly, based on the foregoing differences it is submitted that the references cited in this rejection neither teach nor suggest the presently claimed library. Withdrawal of this rejection is respectfully requested.

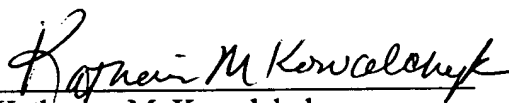
**Conclusion**

Applicants submit the claims are in condition for allowance. Notice of such allowance is earnestly solicited. The Examiner is invited to telephone the undersigned for clarification of any of the amendments and remarks or to otherwise facilitate prosecution of the application.

Respectfully submitted,

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